

HERBAL APPROCHES FOR EPILEPSY: A REVIEW *R. K. Vaya, I. Singhvi, R. Vaya, J. Dwivedi and D. Jain Department of Pharmacology, Pacific College of Pharmacy, Udaipur (Rajasthan)

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ABSTRACT:

The epilepsies are common and frequently devastating disorders, affecting approximately 2.5 million people in the United States alone. More than 40 distinct forms of epilepsy have been identified. Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic in that available drugs do not inhibit seizures, but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many drugs. Although many treatments are available, much effort is being devoted to novel approaches. Many of these approaches centre on elucidating the genetic causes and the cellular and molecular mechanisms by which a normal brain becomes epileptic, insights that promise to provide molecular targets for both symptomatic and preventive therapies.

Keywords: Partial Seizures, Generalized Seizures, Neurobiologic and Neurostimulation.

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INTRODUCTION

Epilepsy may be defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure."

The cause in most cases is unknown, while some are the result of brain trauma, stroke, brain cancer, and drug and alcohol misuse among others. Epileptic seizures are the result of excessive and abnormal cortical nerve cell activity in the brain.

Epilepsy is controllable, but not cured, with medication in about 70% of cases. In those whose seizures do not respond to medication, surgery, neurostimulation or dietary changes may be considered. Not all epilepsy syndromes are life long, and a substantial number of people improve to the point that medication is no longer needed.

About 1% of people worldwide (65 million) have epilepsy, and nearly 80% of cases occur in developing countries. Epilepsy becomes more common as people age.

About 5–10% of all people will have an unprovoked seizure by the age of 80, and the chance of experiencing a second seizure is between 40% and 50%.

In many areas of the world those with epilepsy either have their ability to drive restricted or disallowed. Most however are able to return to driving after a period of time seizure free¹⁻³.

CLASSIFICATION

- 1. Partial seizures (Focal or local seizures)
- a. **Simple partial seizures**: These have various manifestations, without impairment of consciousness. They may include convulsion confined to a single limb.
- b. **Complex partial seizures**: These attacks result in confused behavior, with impairment of consciousness. They have a wide variety of clinical manifestations associated with bizarre generalized EEG activity during the seizure but with evidence of anterior temporal lobe focal abnormalities even in the interseizure period in many cases.
- 2. Generalized seizures (Convulsive or no convulsive)
- a. Absence seizures

- i. **Atypical absence seizures**: Such attacks have a slower onset and cessation than is usual for absence seizures and are associated with a more heterogeneous EEG.
- ii. **Typical absence seizures**: These seizures are brief and abrupt. The resultant loss of consciousness is associated with high-voltage, bilaterally synchronous, 3-per-second spike-and-wave pattern in the EEG, usually with some symmetrical clonic motor activity varying from eyelid blinking to jerking of the entire body, sometimes with no motor activity.
 - b. **Myoclonic seizures**: These are isolated clonic jerks associated with brief bursts of multiple spikes in the EEG.
 - c. **Clonic seizures**: These are rhythmic clonic contractions of all muscles. They result in loss of consciousness and marked autonomic manifestations.
 - d. **Tonic seizures**: Tonic seizures are opisthotonus and result in a loss of consciousness and marked autonomic manifestations.
 - e. **Tonic-clonic (grand mal) seizures**: These are major convulsions, usually a sequence of maximal tonic spasms of all body musculature, followed by synchronous clonic jerking and a depression of all central functions.
 - f. **Atonic seizures**: These are characterized by loss of postural tone, sagging of the head and/or falling²⁻⁴.

Signs and Symptoms

Signs and symptoms depend on the area of the brain in which seizure activity occurs and on the type of seizure. **Symptoms of Simple Partial Seizures**

Symptoms may be motor, sensory, psychic (states of consciousness), and/or autonomic (involuntary activity controlled by the autonomic nervous system). There is no impairment of consciousness in simple partial seizures. While there is a wide range of potential signs and symptoms, for most patients symptoms are stereotypical.

Motor signs include the following:

- Alternating contraction and relaxation of muscle groups
- Eye movements and turning of the head to the same side
- Asymmetrical posturing of the limbs

• Speech arrest, vocalization

Sensory symptoms include the following:

- Seeing flashes of lights or colors, illusions and hallucinations
- Hearing humming, buzzing, hissing noises
- Experiencing unpleasant odors and tastes

• Dizziness, lightheadedness

Autonomic signs and symptoms include the following:

- Borborygmi (rumbling noises produced by gas in the intestines)
- Flushing
- Incontinence
- Nausea, vomiting
- Piloerection (goose bumps)
- Pupillary dilation
- Sweating
- Tachycardia (rapid heart rate)

Psychic symptoms include the following:

- Detachment, depersonalization
- Dreamy state
- Memory distortion: flashback, deja vu (feeling that one has seen something before), deja entendu (feeling that one has heard something before), jamais vu (feeling that one has never seen something that is familiar), jamais entendu (feeling that one has never heard something that is familiar), panoramic vision (rapid recall of past events).
- Time distortion
- Unprovoked emotion: fear, pleasure, displeasure, depression, anger, elation, eroticism^{5, 6}.

Causes

Epilepsy has many possible causes. Because of its complexity, the underlying cause of someone's epilepsy may not be found. Causes of epilepsy can be put into three main groups: symptomatic, idiopathic and cryptogenic epilepsy.

Symptomatic epilepsy

Epilepsy is called 'symptomatic' when it has a known cause. This may include:

- a head injury
- an infection like meningitis
- the brain not developing properly
- a stroke
- a scar
- a tumour.

A scan, such as a Magnetic Resonance Imaging (MRI), may show the cause.

Some symptomatic epilepsies may happen because genetic conditions such as Tuberous Sclerosis, which causes structural abnormalities in the brain and other organs.

Idiopathic epilepsy

Epilepsy is called 'idiopathic' when it is thought to be due to a genetic tendency (which could have been inherited from one or both parents) or due to a change that happens in the person's genes before they are born.

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A genetic tendency to have seizures is likely to be associated with a low seizure threshold. A person's seizure threshold often plays a key role in whether they will develop epilepsy.

Cryptogenic epilepsy

This is when the cause for a person's epilepsy has not yet been found, despite investigations^{7,8}.

MECHANISM

- Two common mechanisms include:
- A. synaptic mechanism
- Diminition of inhibitory mechanism (especially synaptic inhibition due to GABA).
- Enhancement of the excitatory synaptic mechanism (especially those mediated by NMDA).
- B. Non synaptic mechanism
- Enhancement of endogenous neuronal burst firing (usually by enhancing voltage dependent calcium current).

Both nonsynaptic and synaptic mechanisms that affect synchronicity, signal amplification, and spread of seizures play a role during ictal-interictal transition, promoting epileptogenesis⁹⁻¹⁰.

Diagnosis

Your doctor may order several tests to diagnose epilepsy and determine the cause of seizures.

- **Neurological examination** your doctor may test your behavior, motor abilities, mental function and other areas to diagnose your condition and determine the type of epilepsy you may have.
- **Blood tests** your doctor may take a blood sample to check for signs of infections, genetic conditions or other conditions which may be associated with seizures.
- **Electroencephalogram (EEG).** This is the most common test used to diagnose epilepsy. The electrodes record the electrical activity of your brain.
- **Computerized tomography (CT) scan** A CT scan uses X-rays to obtain cross-sectional images of your brain. CT scans can reveal abnormalities in your brain that might be causing your seizures, such as tumors, bleeding and cysts.
- **Magnetic resonance imaging (MRI).** An MRI uses powerful magnets and radio waves to create a detailed view of your brain. Your doctor may be able to detect lesions or abnormalities in your brain that could be causing your seizures.
- **Functional MRI (fMRI)**. A functional MRI measures the changes in blood flow that occur when specific parts of your brain are working. Doctors may use an fMRI before surgery to identify the exact locations of critical functions, such as speech and movement,

so that surgeons can avoid injuring those places while operating.

- **Positron emission tomography (PET).** PET scans use a small amount of low-dose radioactive material that's injected into a vein to help visualize active areas of the brain and detect abnormalities.
- **Single-photon emission computerized tomography (SPECT).** This type of test is used primarily if you've had an MRI and EEG that didn't pinpoint the location in your brain where the seizures are originating¹¹⁻¹².

Prevention

If the seizures are related to another medical condition, identification and treatment of that medical condition is the key to prevention. If anticonvulsant medication is prescribed, taking the medication on the recommended schedule and not missing medication is important.

- Some people with epilepsy are quite sensitive to alcohol. If this pattern develops, avoid alcohol. Others may have seizures only after ceasing heavy alcohol intake. The key to prevention is avoidance of alcohol.
- Sleep deprivation and stress certainly may increase the frequency of seizures in some people with epilepsy¹³⁻¹⁴.

HERBAL THERAPIES FOR EPILEPSY

Historical evidence suggests that herbal therapies were used to treat convulsive seizures as early as 6000 BC in India, with the origin of Ayurveda, and 3000 BC in China and in Peru; similarly, Africa and South America have rich traditions in herbal therapies, including for convulsions. The Ayurvedic literature contains treatises on epilepsy- like symptoms, causes, recognition, and treatment. Herbal and dietary therapies, which are recommended for external application, internal use, and topical use in the eves and nose, include Brahmirasayan, Brahmighritham, Ashwagandha, old pure desi ghee, daily fresh juice of brahmi (Centella asiaticaor Bacopa species, among others) with honey, garlic juice in oil, and powdered root of wild asparagus (Asparagus racemosus) with milk. Others are Acacia nilotica (syn. Acacia, Arabica), Acorus calamus, Bacopa monnier, Clitorea ternatea, Celastrus paniculatus, Convolvulus pluricaulis, Phyllanthus emblica (syn. Emblicaofficinalis), mukta pishti (processed from pearls of Mytilus magaritiferus mussels), Withania somnifera. Recent scientific publications provide the scientific rationale for proceeding with controlled trials of some of these herbal therapies in patients with epilepsy¹⁵⁻¹⁷. Herbal therapies used to treat convulsive diseases in Asia in modern times include Chai-Hu-Long-Ku-Mu-Li-Tan (TW-001), a mixture of extracts from herbal

therapies; Gastrodiaelata (Tian Ma; gastrodia root); Uncaria rhynchophylla (cať s claw): Menispermumdauricum (moonseed); Shitei-To, a mixture of extracts from three medicinal herbs, Shitei (kaki calvx: the calvx of Diospyros kaki persimmon). Shokyo (ginger root: rhizome of Zingiber officinale). and Choji (clove; pharmaceutical name, caryophylliflos; the flower bud of Syzygium aromaticum); mixture of radish (Raphanus sativus) and pepper (Piper species. containing the alkaloid piperine); Qingyangshen (root of Cynanchumotophyllum); Kanbaku-taiso-to, a mixture of three herbal drugs, glycyrrhizae radix (licorice root; Glycyrrhiza species), tritici semen (wheat seed; Triticumae stivum), and zizyphi fructus (spiny jujube fruit; Ziziphus spinosa); paeoniae radix (peony root; Paeonia lactiflora, synonym P. albiflora); and Zheng Tai instant powder (a complex prescription of traditional Chinese medicines used for tonic- clonic seizures). Several of these herbal therapies have been shown to have neuroprotective properties, efficacy in animal models of epilepsy and hippocampal slice models, and effects on gene expression. These studies generally do not specify, however, the methods used to 1) authenticate the source plants, 2) produce extracts BOTANICALS AND HERBS 417 and fractions, 3) characterize the active ingredients, or 4) perform the Table 1. Plant and their use in Enilensy treatment¹⁶⁻⁴²

preclinical evaluations.43 recent investigations have addressed these limitations.

In 2005, a comprehensive literature search identified 3 randomized controlled trials, 5 nonrandomized controlled trials, 6 case– control studies and 57 observational studies, including case reports, of herbal therapies from the East Asia for the treatment of epilepsy. 53 More than 135 different herbal extracts were used individually or in various combinations (formulas) in these studies, although rarely was the same herbal formula used in more than one study¹⁵.

CONCLUSION

In last few decades there has been exponential growth in the field of herbal medicine and their used in treatment of various disease. In this article we explain the used of plant in treatment of epilepsy. Epilepsy is widely affected in world and their treatment is also affect humans body. So that's why herbal treatment is best approaches for its treatment. So we are tried to gather some knowledge in this article.

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	Table 1: Plant and their use in Epilepsy treatment ¹⁶⁻⁴²					
S. No		Active Constituent		Remarks	Mechanism Of Action	
	manihot (Malvaceae)	Flower. Isoquercitrin, hyperoside, hibilfolin, quercetin-3-o- glucoside, quercetin.		manihot ethanol extract could protect	It explores the activity on the central nervous system. Anticonvulsant and antidepressant-like activity in vivo.	
	Acorus	Rhizome. Asarone, ursolic acid.	induced convulsion MES induced convulsion	exacerbated tonic seizures provoked by metrazole in rats. The .aqueous and the alcoholic extracts reduce the severity of MES induced seizures in rats.	Anticonvulsant activity by decreasing the duration of tonic extensor phase.	
	0	Water extract of rhizome. Essential oils, asarones, 1-allyl-2,4,5 Trimethoxybenzene, lignans.	PTZ induced convulsion.	A.gramineus at dose 5g/kg has anticonvulsant effect against PTZ induced seizures.	It inhibits the activity of hippocampal neurons and produces antiepileptic effect in central nervous system through enhancing tonic GABAergic inhibition.	
	Aegle marmelos (Rutaceae)	compounds and alkaloids.	convulsion MES induced convulsion	onset time and decreases the duration of seizures by electro convulsive shock. The study also revealed that the onset of tonic convulsant produced by PTZ was significantly delayed and also duration of seizures was prolonged.	inhibitory effect on [³ H] glutamate binding in rat cortex membranes.	
-		Lyophilized root decoction. α-methyldeoxy benzoins angolensin, 2-	convulsion MES induced	Doses of 150-300mg/kg of extract significantly diminished the duration of convulsive symptoms and increase the seizure latency in both PTC and	Significant inhibition of motor activity in mice, indicating depressant actions. Significantly diminished the duration of convulsive symptoms, and increased the	

		o-methyl-angolensin &		MES induced seizure when compared	seizure latency.
		demethylpterocarpin.		with controls.	
6.	Alangium salvifolium (Alangiaceae)	,	PTZ induced convulsion MES induced convulsion.	Ethanol extract exhibited significant (p<0.01) antiepileptic activity.	It reduced the duration of seizures produced by maximal electroshock as well as delayed the latency of seizures.
7.	Albizzia lebbeck (Mimosaceae)	leaves. flavonoids, tannis and saponins.	MES induced convulsion Kindled rat seizure model PTZ induced convulsion.	Alcoholic extract of leaves of A. lebbeck showed anticonvulsant effect in MES and PTZ induced convulsions.	It raised brain contents of gamma- aminobutyric acid (GABA) and serotonin. These were found to be anxiogenic and general depressant of central nervous system.
8.	Ambrosia paniculata (Asteraceae)	leaves.	convulsion, Isoniazid induced convulsion.	a decoction of the dried leaves significantly enhanced the latency to the first convulsion and survival time in mice injected with PCT (7mg/kg) or isoniazid (210mg/kg).	
9.	American ginseng (Araliaceae)		convulsion Pilocarpine induced convulsion.	40-60 mg of the extract has significant effect on pilocarpine and PTZ induced seizures.	It increases the latency to the seizures; decreases the seizure score, weight loss, and subsequent neuronal damage.
10.	Anisomeles malabarica (Lamiaceae)	Flavonoids fraction and	convulsion	Pretreatment with A. malabarica (25 and 50 mg/kg i.p.) has found to be effective against both MES and PTZ convulsions.	It acts by marked decrease in locomotor activity and motor activity performance.
11.	Annona diversifolia (Annonaceae)		Penicillin induced seizures.	The extract is effecting in reducing the severity of behavioural and EEG seizures induced by penicillin in rats.	It increases the latency to the onset of spikes and seizures.
12.		extract(́HE). α-thujone and camphor.	convulsion MES induced convulsion Pilocarpine model 3-Nitro-	High doses of HE (2g/kg) prevented the onset of electroshock (75mA, 60Hz) and PTZ induced (75mg/kg i.p.) convulsions and also increases the latencies to convulsions induced by 3-nitropropionic acid (30mg/kg i.p.) and pilocarpine (400mg/kg i.p.) in mice.	It prevented the onset of electroshock. As an anticonvulsant and analgesic.
13.	dracunculus	anethole (21.1%), α-	convulsion	The essential oil exerted dose dependent and time dependent anti seizure activity in both MES and PTZ models of experimental seizures with ED50 values of 0.84 and 0.26ml/kg respectively.	Anticonvulsant and sedative effects could be related to the presence of monoterpenoids in the essential oil.
14.	Astragalus mongholicus (Leguminosae)		PTZ induced convulsion.	The behavioural showed that the root extract of A.M. had powerful anticonvulsant effect against seizures induced by PTZ.	Anti-convulsant effects of AM may be mediated by its protective actions against oxidative damage and amelioration of mitochondrial dysfunction.
15.	Bacopa monnieri (Scrofulariace ae)	Whole plant Bacoside-A.	Pilocarpine induced epilepsy.	The plant has significant antiepileptic activity.	Anti-convulsive effects could be mediated through GABA which is involved in neural impulse transmission, because substances which stimulate GABA are known to possess anticonvulsant, pain relieving and sedative activities.

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	roxburghii (Simarubaceae	Pericarpium saponin glycosides, flvonoids, tannins, alkaloids, phenols.	MES induced convulsion PTZ induced convulsion	This studies shows that B.R. significantly increases the onset time and decreases the duration of seizures by electroconvulsive shock.	It significantly increases the onset time and decreases the duration of seizures by electroconvulsive shock. saponins and flavonoids present in B. roxburghii might contribute to the anticonvulsant activity of the plant.
	(Balanitaceae)	Palmitic, stearic, oleic and lenoleic acids.	PTZ induced convulsion PTX induced convulsion.	The decoction protected mice against PTZ induced seizures, but had no effect on PTX induce seizures.	The extract of Balanites aegyptiaca possess biologically active compound(s) that have anxiolytic and sedative properties, which support the ethnomedicinal use of the plant as antipsychotic and antiepileptic agents.
		Root Scopoletin.	STR induced convulsion Isoniazid induced convulsion.	It demonstrated 30% and 35% protection against strychnine induced convulsions and 60% and 80% protection against isoniazid induced convulsions, at doses of 25mg/kg and 50mg/kg respectively.	Benkara malabarica extract possesses GABA-T inhibitory activity so used as a anticonvulsant.
19.	(Bixaceae)	Methanolic extract of leaves. Farnesyl acetate, occidentalol acetate.	STR induced convulsion.	In the STR induced anticonvulsant test, the extract increased the average survival time of the test animals.	It produced a significant anticonvulsant activity after 30 minutes in the dose of 200 mg/Kg body weight.
		Essential oil and methanolic extract.	PTZ induced convulsion MES induced convulsion.	The essential oil and methanolic extract prolonged the onset action of clonic and tonic seizures in PTZ.	The essential oil (Monoterpene) of the plant might be useful to control absence and grand mal seizures.
	Caesalpinia pulcherrima (Fabaceae)	Leaves	PTZ induced convulsion MES induced convulsion.	The plant has significant antiepileptic activity.	This plant must be investigated to isolate the phytoconstituent responsible for anticonvulsant effect as well as its mechanism.
22.	sappan (Leguminosae	80% aqueous MeOH extracts of wood. Sappanchalcone and brazilin.		80% aqueous extracts from the wood of C.S., showed remarkable anticonvulsant activity.	It significantly inhibited the activities of two GABA degradative enzymes, succinic semialdehyde dehydrogenase (SSADH) and succinic semialdehyde reductase (SSAR).
23.	officinalis (Lamiaceae)	Essential oil carvone, neo-dihydrocarveol, dihydrocarveol acetate, dihydrocarveol, 1,8 cineole and pulegone.	PTZ induced convulsion	C.O. essential oil provides protection against pentylene tetrazole-induced convulsions.	It produces a decrease in body temperature and a protection against pentylenetetrazole-induced convulsions.
24.	Calliandra portoricensis (Leguminosae)		convulsion	The aqueous extract of root and stem possess anticonvulsant activity in PTZ and MES induced convulsions.	
25.	Calotropis gigantia (Asclepiadacea e)	Alcoholic extract of roots.	PTZ induced convulsion.	Significant anticonvulsant activity was seen as there was delay in onset of PTZ induced convulsions as well as decrease in severity.	C. procera latex proteins have a central nervous system-depressant activity as reflected in their potentiation of pentobarbital-induced sleeping time and their anticonvulsant action in the PTZ- induced seizure.
	deciduas (Capparidacea e)		convulsion MES induced convulsion.	decidua extract dose dependently decreased (P<0.05) the number of animals with convulsions and increased convulsion latency(P<0.001)	C. decidua has CNS depressant and anticonvulsant activities.
27.	Carissa edulis (Apocynaceae)	-	MES induced convulsion	Carissa edulis exhibited dose dependent inhibition of the convulsion induced by MES test with	Carissa edulis possesses biologically active constituent(s) that have anticonvulsant activity which supports

				20mg/kg providing 90% protection.	the ethnomedicinal claims of the use of the plant in the management of epilepsy.
28.	copticum (Umbelliferae)		convulsion.	delayed the incidence of every seizure stage in the PTZ model of kindling.	CCS extract has remarkable antiepileptic and central depressant effects.
29.	Casimiroa edulis (Rutaceae)	Aqueous extract of leaves.			Potencially antiepileptic compounds are present in C. edulis extracts that deserve the study of their identity and mechanism of action.
30.	Cassia sophera (Caesalpiniace ae)	seed.	convulsion MES induced convulsion.	Test drug (440mg/kg) produced significant anticonvulsant effect against hind limb tonic extension phase of maximum electroshock induced seizure test and seizures induced by PTZ.	It useful in both types of epileptic conditions viz., grand mal and petit mal epilepsy.
31.	Cedrus deodara (pinaceae)			The plant has significant antiepileptic activity.	Anticonvulsant activity by enhancing inhibitory GABAminergic neurotransmission.
32.	coromendelian	steroids.	convulsion Leptazol induced convulsion.	strychnine and leptazol induced convulsion.	The presence of steroids and saponins might be responsible for respective CNS activities.
33.	Centella asiatica (Umbelliferae)	Leaves	PTZ induced convulsion	has perceptible anticonvulsant activity.	The activities of three ATPases were decreased in different regions of brain. It possesses anticonvulsant and neuroprotective activity and thus can be used for effective management in treatment of epileptic seizures.
34.	Clerodendron infortunatum (Lamiaceae)		convulsion STR induced convulsion		It decrease the duration of seizures and gave protection in a dose dependent manner. saponin has significant analgesic and anticonvulsant effects.
35.	Clitoria ternatea (Leguminosae)	Metanolic extract.	convulsion.		The extract was found to possess nootropic, anxiolytic, antidepressant, anticonvulsant and antistress activity. Further studies are necessary to isolate the active principle responsible for the activities and to understand its mode of action.
36.		methanolic extract of leaves.	convulsion	(100-400mg/kg,i.p.) significantly	Cotyledon orbiculata have anticonvulsant property and may probably be affecting both gabaergic and glutaminergic mechanisms to exert its effect.

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